

REMARKS

Upon entry of the foregoing amendments, claims 4, 5, 7, 12, 13, 15, 16 and 32-37 will be pending in the application. Claim 37 is the only independent claims.

Explanation of and Support for the Amendments

Previously pending claims 1, 3, 8-11, 14 and 17-19 have been cancelled without prejudice to focus the remaining claims on presently preferred aspects of the present invention.

Claim 1 has been replaced by new independent claim 37 directed to a composition in the form of an aqueous solution for nasal delivery of zolpidem or a pharmaceutically acceptable salt thereof, wherein the composition comprises: (a) 16 to 97 mg/ml of zolpidem (expressed as the free base); (b) sulfobutylether β -cyclodextrin (SBE-CD); and (c) chitosan, a salt, or a derivative thereof or a salt of a derivative thereof.

Compared to claim 1, claim 37 recites that the composition is an aqueous solution, supported at least by original claim 3. The amount of zolpidem or a pharmaceutically acceptable salt thereof is recited as being 16 to 97 mg/ml, expressed as the free base), as supported at least at page 3, line 15, of the application as filed (all references to the "application as filed" refer to the Substitute Application filed June 26, 2006). Claim 37 also recites that the composition comprises SBE-CD and chitosan, a salt, or a derivative thereof or a salt of a derivative thereof. SBE-CD is supported at least by claim 11 of the application as filed. Chitosan, a salt, or a derivative formed by bonding acyl and/or alkyl groups with the hydroxyl groups, but not the amino groups of chitosan or a salt of a derivative thereof is supported at least by original claim 14 of the application as filed. The characterization of the chitosan derivative is supported at page 27, lines 25-28 of the application as filed.

Claims 4, 7, 12, 13, 15, 16, 32-34 and 36 have been amended to change their dependencies from cancelled claims so as to depend now from independent claim 37.

Since the amendments are fully supported by the application as filed and contain no new matter, entry of the foregoing amendments is respectfully requested.

Response to Restriction Requirement

In this Office Action, the Examiner has entered a restriction requirement involving the following five invention Groups:

Group I: Claims 1, 3-5 and 7-19 (now, after the foregoing amendment, claims 37 and its directly or indirectly dependent claims 4, 5, 12, 13, 15 and 16), drawn to a composition in the form of an aqueous solution for nasal delivery of zolpidem or a pharmaceutically acceptable salt thereof;

Group II: Claim 32, drawn to a method of intranasal administration of the composition of claim 37;

Group III: Claim 33, drawn to a method of treating or preventing insomnia by intranasally administering the composition of claim 37;

Group IV: Claims 34 and 35, drawn to a method of treating a neurological disorder or Parkinson's disease by intranasally administering the composition of claim 37; and

Group V: Claim 36, directed to a nasal drug delivery device.

The Examiner took the position that the indicated groups do not relate to a single general inventive concept under PCT Rule 13.1, because under PCT Rule 13.2, they lack the same or corresponding special technical features, even though the Examiner acknowledged that all groups recite explicitly or by depending from claim 37, directly or indirectly, a composition in the form of an aqueous solution for nasal delivery of zolpidem or a pharmaceutically acceptable salt thereof. The Examiner determined that such a composition cannot be a special technical feature in view of the Examiner's interpretation of Kramer, *et al.* US Patent Application Publication No. US 2004/0241100 ("Kramer"), which the Examiner considered renders the composition unpatentable.

Applicants respectfully traverse the restriction requirement for the following reasons.

Initially, as set forth in detail below, Kramer does not teach or suggest the composition or any of the other aspects of the invention claimed in any of Groups I to V. Therefore, all of the invention groups have the same or a corresponding special technical feature.

Further, PCT Rules 13.1 and 13.2 have criteria that are substantially identical to 37 CFR § 1.475(a). According to 37 CFR § 1.475(b), which is also applicable to the present invention as a national stage application of an International PCT application under 35 USC § 371, products

and processes (methods) for use of the product (37 CFR § 1.475(b)(2)) and a process and apparatus specifically designed for carrying out the process (37 CFR § 1.475(b)(4)) are considered to have unity of invention.

Here, all of the process (method) claims of Groups II to IV and the device claim of Group V depend directly or indirectly from independent composition claim 37. Therefore, the components of composition claim are incorporated by reference into the other dependent claims.

A reasonably thorough search and examination of the composition would lead to disclosures of processes (methods) for using the composition and for devices to administer the composition. Therefore, such a search of the composition, the methods of use and the device for administering the composition would not be a significant burden, if any, for the Examiner in view of the language of the methods of the invention, as claimed.

The Courts have stated that Applicants are permitted to claim several aspects of the invention in one application, as the Applicants have done here. For example, in a case where a product, a process of making the product and a process for using a product were claimed, the Court *In re Kuehl*, 475 F.2d 658, 666, 177 USPQ 250, 256 (CCPA 1973), has stated:

We believe the constitutional purpose of the patent system is promoted by encouraging applicants to claim, and therefore to describe in the manner required by 35 U.S.C. § 112 all aspects as to what they regard as their invention, regardless of the number of statutory classes involved.

This interest is consistent with the practical reality that a sufficiently detailed disclosure supporting claims to one aspect of the invention customarily is sufficient to support claims in the same application to other aspects of the invention. This admonition is eminently appropriate in the present application.

For the reasons set forth above, the Examiner is respectfully requested to reconsider and withdraw the restriction requirement and to search and examine all of the pending claims in the present application.

Provisional Election of Claims

If the Examiner does not withdraw the restriction requirement, Applicants hereby confirm the undersigned attorney's oral provisional election, with traverse, of June 1, 2010, for

prosecution in this application, with the traverse as noted herein above, the subject matter of Group I, namely composition claims 4, 5, 12, 13, 15, 16 and 37.

Furthermore, as noted at pages 5-6 of the Detailed Action, since the Office Action required restriction between product and process of using claims and Applicants elected the product claims, if a product claim is subsequently found to be allowable, any withdrawn process claim that depends from the allowed product claim will be rejoined as a matter of right in accordance with MPEP § 821.04. To assure that this rejoinder of right is satisfied, Applicants respectfully request the Examiner to rejoin claim 32 of Group II, claims 33 and 34 of Group IV and claim 35 of Group IV when at least one of the composition claims of Group I is found to be allowable.

Rejections Under 35 USC § 112

At pages 6-7 of the Detailed Action, the Examiner rejected various claims on the basis of a typographical error in claim 1 reciting an upper limit of .97 (more clearly 0.97), rather than 97, mg/ml of zolpidem or pharmaceutically acceptable salt thereof (expressed as the free base). This typographical error has been corrected in new independent claim 37. Accordingly, the rejections under 35 USC § 112, first and second paragraphs, are moot and Applicants respectfully request that they be reconsidered and withdrawn.

Anticipation Rejection Under 35 USC 102(e)

Claims 1, 3-5, 7-9, 13, 14, 18 and 19, all of which, except claims 4 and 5 are now cancelled, were rejected under 35 USC § 102(e) as being anticipated by Kramer.

However, before addressing the points raised by the Examiner, it would be useful to provide some general information on cyclodextrins and drug delivery, as noted in paragraph 9 of Dr. Castile's Declaration. The use of cyclodextrins in formulation science is well established, primarily to increase the solubility of poorly-soluble drug compounds. Cyclodextrins can increase drug bioavailability by solubilising an otherwise insoluble drug and thus delivering it to the absorption site in dissolved form. However, for a drug which has reasonable, but not high, aqueous solubility, the situation can be more complicated. Cyclodextrin molecules adopt a cone-like structure in aqueous solution, with a relatively hydrophilic (water soluble) exterior and

hydrophobic interior cavity. The hydrophobic drug molecule will form an inclusion complex within the interior cavity of the cyclodextrin molecule and it will need to partition out of the cyclodextrin and, subsequently, diffuse across the mucosal membrane in order to be absorbed. Consequently, depending on the affinity between the drug and cyclodextrin molecules, it could be that absorption of drug from a cyclodextrin formulation is impaired relative to a simple solution, and although the cyclodextrin may allow a larger dose of drug to be administered, the proportion of the drug absorbed could be reduced.

As paragraph 9 of Dr. Castile's Declaration further points out, this means that the effect that a given cyclodextrin has on the pharmacokinetic properties of a drug will vary from one drug to another, particularly if the drugs are unrelated. Thus, information about the effect a cyclodextrin has with one drug is not predictive for another unrelated drug. Moreover, different cyclodextrins are also likely to give different effects, including pharmacokinetic effects and solubilisation potential for different molecules, in that the effects of SBE-CD are not predictable from other cyclodextrins, such as hydroxypropyl- β -cyclodextrin or randomly-methylated β -cyclodextrin.

Further, as noted in paragraph 10 of Dr. Castile's Declaration, the inclusion of other components, such as chitosan, into a composition containing cyclodextrins such as SBE-CD, further complicates the unpredictable nature of how a drug's pharmacokinetics may be affected when administered to a subject. For example, it can be envisaged that there will be competing interactions between the different formulation components, potentially affecting the quantity of free drug available for absorption across the mucosal surface and the speed at which absorption occurs. Kramer describes compositions for nasal administration which include zolpidem, a prodrug thereof, a pharmaceutically acceptable salt thereof, or a combination thereof, and a pharmaceutically acceptable nasal carrier in liquid form.

There is a suggestion in paragraph [0036] of Kramer that the compositions described therein could comprise "chitosan hydroxycellulose." It is believed that there is no known compound called "chitosan hydroxycellulose." (Dr. Castile Declaration, paragraph 22). Moreover, there is no explicit disclosure of a composition containing chitosan, and there are no working examples set forth in Kramer, and no specific embodiments are disclosed of a composition containing chitosan.

Kramer most certainly does not provide an explicit and enabling disclosure of a composition in the form of an aqueous solution for the nasal delivery of zolpidem or a pharmaceutically acceptable salt thereof comprising chitosan, a salt or a derivative thereof or salt of a derivative thereof. The claimed composition of the present invention is novel for this reason alone.

In addition, it is an essential feature of the amended claims that the composition comprises both SBE-CD and chitosan, a salt, or a derivative thereof, or a salt of derivative thereof. There is absolutely no disclosure or suggestion in Kramer that a cyclodextrin could be or should be used in the compositions it describes, let alone that a suitable cyclodextrin would be SBE-CD. Still less is there any suggestion that chitosan could be or should be used in combination with a cyclodextrin. Thus, for this reason, the composition of the present invention defined by claim 37, the only remaining independent claim, is novel in view of Kramer.

Since Kramer does not disclose all of the components claimed in claim 37, Kramer fails as an anticipating reference. Applicants respectfully request reconsideration and withdrawal of the anticipation rejection under 35 USC § 102(e) over Kramer.

Obviousness Rejections Under 35 USC § 103(a)

The Examiner rejected claims 10, 11 and 12, of which only claim 12 remains pending, on the grounds of obviousness over Kramer in view of Auh, *et al.* European Patent EP 1 250 925 ("Auh"). Auh describes nasal spray compositions comprising ondansetron hydrochloride.

The Examiner repeated a summary of the disclosure of Kramer, and concluded that regarding these claims, which include SBE-CD, Kramer is only lacking a disclosure of SBE-CD, which the Examiner asserts is supplied by Auh.

Independent claim 37 now recites a composition in the form of an aqueous solution for nasal delivery of zolpidem or a pharmaceutically acceptable salt thereof, wherein the composition comprises: (a) 16 to 97 mg/ml of zolpidem (expressed as the free base); (b) sullobutylether β -cyclodextrin (SBE-CD); and (c) chitosan, a salt, or a derivative formed by bonding acyl and/or alkyl groups with the hydroxyl groups, but not the amino groups of chitosan

or a salt of the derivative thereof. Therefore, to the extent that the combination of Kramer and Auh would be applied against claim 37, Applicants address this consideration.

As noted above, Kramer does not disclose a chitosan, a salt, or a derivative thereof or a salt of a derivative thereof, but merely incidentally discloses among many other ingredients, a chitosan hydroxycellulose in paragraph [0036], a compound which is believed not to exist. Even if such a compound does exist and even if chitosan and hydroxycellulose were intended to be presented as separate components, the Kramer disclosure is not an enabling disclosure.

Moreover, even if a skilled person decided to follow the teaching of paragraph [0036] of Kramer and use a mucoadhesive in the composition of Kramer, the skilled person would have had a choice of no less than five listed mucoadhesives (which are merely examples of mucoadhesives that could be used). However, in the absence of any examples or more specific embodiments in Kramer, there is nothing to motivate the skilled person to select any one of the many possible ingredients in preference to any other ingredient.

There is nothing in the teaching of Kramer alone that would have motivated the skilled person to produce a composition comprising the combination of ingredients that is claimed in claim 37. The claimed compositions are therefore not obvious in view of the teaching of Kramer. This must have been appreciated by the Examiner, who combined Kramer with Auh in the obviousness rejection. There is nothing in Auh to provide the missing motivation or suggestion to combine Kramer's composition with only one of several essential ingredients of Auh's composition.

There are very distinct advantages, unrecognized by those skilled in the art prior to the present invention, including Kramer and Auh, associated with using chitosan in combination with SBE-CD in an aqueous composition for the nasal delivery of zolpidem. As explained at page 3, fourth paragraph, of the present application as filed, relatively high concentrations of zolpidem are required in order to effectively treat insomnia using a composition delivered via the intranasal route. The concentrations required are above the reported aqueous solubility of zolpidem tartrate as published in the Merck Index (Dr. Castile Declaration, paragraph 16 and Exhibit B). It has been found that the inclusion of SBE-CD in the compositions of the invention enhances the aqueous solubility of zolpidem (and its salts). This means that compositions

comprising zolpidem in a concentration suitable for nasal delivery for the treatment of insomnia can be provided.

As pointed out in Dr. Castile's Declaration, paragraph 17, it is particularly important when producing a composition for nasal delivery that the drug is present in the solution at a suitably high concentration. This is because, due to the nature of the nasal cavity, there is a limit to the amount of liquid that can be administered at one time. As discussed at page 13, lines 26-31, of the present application, in practical terms it is only possible to administer up to about 0.2 ml of solution to each nostril. Thus, it is necessary to ensure that sufficient drug to provide the required therapeutic effect is contained in this amount, or less, of solution.

It is also desirable to avoid using a saturated solution of the drug (Dr. Castile's Declaration, paragraph 18). Saturated solutions contain the maximum amount of dissolved drug possible at a given temperature. Changes in storage conditions, such as changes in temperature, can result in precipitation of the drug. This is undesirable because it could reduce the amount of drug delivered when the solution is used. In other words, the use of a saturated solution would result in inconsistent and unreliable drug dosing. This is clearly highly undesirable. The present invention avoids these issues by enhancing the solubility of zolpidem in aqueous solution.

Additionally, the inclusion of chitosan in the compositions of the invention increases the bioavailability of the zolpidem. See Example 5 of the present application.

The combination of increased drug solubility and improved bioavailability provides an aqueous composition that can be very effective for the treatment of conditions such as insomnia.

The compositions described in Auh comprise a complex base material consisting of (i) 70 to 85% by weight of water, (ii) 5 to 15% by weight of polyethylene glycol, (iii) 0.005-0.02% by weight benzalkonium chloride and (iv) 7 to 20% by weight of one stabilizer selected from SBE-CD sodium salt, dimethyl- β -cyclodextrin and 2-hydroxypropyl- β -cyclodextrin. It is clear from the disclosure of Auh that this disclosed combination of the ingredients of the base material is required in order to give the compositions described in Auh the required properties. See, for example, paragraph [0016] of Auh. The skilled person reading Auh would not have contemplated moving away from Auh's essential teaching and selecting just one of the essential ingredients of the base material to use in these compositions.

Additionally, it is noted that ondansetron is a completely different drug compared to zolpidem. The drugs may share a feature in that neither is highly soluble in aqueous solution. However, this does not mean that the skilled person would have expected that a means of improving the solubility of ondansetron would also be effective to improve the solubility of zolpidem without in some way affecting other properties of the drug, such as its pharmacological efficiency. As discussed above, the interaction between the drug and the cyclodextrin is very dependent on the nature of the drug and the nature of the cyclodextrin used. The skilled person would not have considered the information provided in Auh about ondansetron to be predictive for zolpidem.

Exhibit C to Dr. Castile's Declaration summarises some of the most important differences between zolpidem and ondansetron, including the differences in chemical structure. (Dr. Castile's Declaration, paragraph 19).

Applicants' assignee Archimedes Development Limited, has conducted a study, under the direction and supervision of Dr. Jonathan Castile, one of the inventors named in the present application, to evaluate the effect that the combination of a chitosan and a cyclodextrin have on the properties of ondansetron (Dr. Castile Declaration, paragraph 11). A write-up of the study is set forth in Dr. Castile's Declaration, paragraphs 12-14. The resulting data of this study show that the inclusion of a cyclodextrin in an ondansetron-containing solution improved the bioavailability of ondansetron. However, when a combination of a chitosan and cyclodextrin was used, the bioavailability decreased. Thus, there was no advantage in using the combination of a chitosan and a cyclodextrin where ondansetron is the active ingredient. (Dr. Castile's Declaration, paragraph 14).

As noted in Dr. Castile's Declaration, paragraph 15, the results of the study are significantly different from the experimental results reported in the present application, and demonstrate the unpredictable nature of the use of cyclodextrins and chitosan in combination with various drugs. Table 3 of the present application reports the bioavailability of a composition of the invention (Example 4) versus a composition using zolpidem and SBE-CD (Example 3) and an aqueous saline solution of zolpidem (Example 5). The solution of Example 4 contained both SBE-CD and chitosan glutamate and shows a significant improvement in bioavailability compared to Example 3, which contained SBE-CD but no chitosan. This is

surprising and unexpected and could not have been predicted from the information about ondansetron provided in Auh or as set forth in the study.

The Examiner has also referred to Birch, *et al.* WO 03/080021 A2 ("Birch"), in rejecting claims 1, 3-5, 7-10, 13-15 and 17-19. Dr. Castile is named a co-inventor in Birch, which was further combined with the teaching of Kramer and Auh. Birch describes compositions comprising buprenorphine and a low DE pectin or a chitosan together with a hydroxypropylmethylcellulose (HPMC) or chitosan and a poloxamer. As the Examiner has noted, Birch at page 19, lines 16 to 20, also discusses the possibility of the compositions it describes comprising an absorption promoting agent such as cyclodextrin.

Again, buprenorphine is a completely different drug compared to zolpidem and the skilled person would not have expected that teaching relating to buprenorphine could necessarily be applied to zolpidem. Exhibit D to Dr. Castile's Declaration summarises some of the most important differences between zolpidem and buprenorphine, including the differences in chemical structure. (Dr. Castile's Declaration, paragraph 20).

It is an essential feature of Birch that the compositions comprising chitosan also comprise a poloxamer or hydroxypropylmethylcellulose. A skilled person reading Birch would not have even contemplated using chitosan in the absence of one or other of these ingredients, let alone replacing these ingredients with SBE-CD. This would go against the basic and essential teaching of Birch.

Additionally, it is noted that according to the disclosure of Birch, cyclodextrin may be used as an absorption promoting agent. Birch does not provide any information that would have suggested to the skilled person that any cyclodextrin could be used as a solubility enhancing agent for zolpidem. There is certainly no suggestion that SBE-CD could have this effect.

When working on the compositions of the invention, the teaching of Birch that cyclodextrins can be used as absorption promoting agents would not have encouraged the skilled person to use cyclodextrins because chitosan is used to enhance bioavailability so another material having a similar function would not be required. There is certainly nothing in Birch to suggest that chitosan and SBE-CD could successfully be used together to enhance solubility and improve bioavailability.

The Examiner has also rejected claims 1, 3-5, 7-10, 13-15 and 17-19 on the grounds of obviousness over Birch in view of Liu, *et al.* International Application Publication No. WO 03/095498 A1 (in Japanese) as understood based on its equivalent US Patent Application Publication No. US 2005/0215520 ("Liu").

As discussed above, the teaching of Birch is not highly relevant to the present invention. Birch is concerned with the completely unrelated drug, buprenorphine. The comments above relating to the disclosure of Birch also apply to this rejection.

Liu describes a process of preparing a water-soluble complex of water-insoluble or sparingly soluble organic medicines and β -cyclodextrin derivatives. There is, however, no disclosure or suggestion of the use of SBE-CD. Thus, to arrive at the present invention from the combination of Birch and Liu, the skilled person would have had to replace the buprenorphine of Birch by zolpidem, select chitosan in preference to the other excipients mentioned in Birch, remove the poloxamer or hydroxypropylcellulose that is used in combination with the chitosan in Birch and replace it by a cyclodextrin that is not even suggested in Liu. This is well beyond what could be expected from a person of ordinary skill in the art. Again, it is important to note as set forth in Dr. Castile's Declaration (paragraphs 8-11, 15 and 21) that the effects achieved by the combination of one drug with a given cyclodextrin are not predictive of the effects that cyclodextrin would have on a different drug, and most certainly not predictive of the effects that a different cyclodextrin would have on a different drug.

The Examiner raised an obviousness rejection of claims 1, 3-5, 7-10, 13-15 and 17-19 over Loftsson, *et al.* US Patent 6,699,849 ("Loftsson"), in view of Kramer. Loftsson describes a method for enhancing the complexation efficiency of a benzodiazepine with a cyclodextrin. The conditions used in Loftsson are designed to "ring open" a proportion of the benzodiazepine molecules in order to optimise complexation. There is no mention of zolpidem or of compounds with a similar structure to zolpidem. There is nothing in Loftsson to suggest that zolpidem could undergo "ring opening" under the condition used in Loftsson, or even that this would be desirable. The disclosure of Loftsson seems completely irrelevant to the present application.

The Examiner noted that Loftsson lacks a specific disclosure of the addition of chitosan and of the use of zolpidem as the active agent, but nevertheless considers that these deficiencies are cured by Kramer. As discussed above, Kramer does not provide an enabling disclosure of a

composition for nasal delivery comprising zolpidem and chitosan. Thus, the combination of Loftsson and Kramer does not render the present invention obvious, even assuming that these references are properly combinable.

As pointed out in paragraph 8 of Dr. Castile's Declaration, after summarizing the obviousness rejections in paragraphs 6 and 7, pharmaceutical and drug delivery research is not conducted in reality as apparently considered by the Examiner, namely, in hindsight, by later picking and choosing various ingredients from among other compositions including other drugs and other components from references, against the background of a successful invention. Instead, such research is generally conducted, and was conducted concerning the present invention, by starting with a goal, here how to better deliver zolpidem intranasally to have the desired pharmacokinetic properties ultimately achieved by the present invention after considerable experimentation in view of the unpredictable effects regarding zolpidem as the active ingredient in combination with SBE-CD and chitosan.

In view of the unpredictable nature of the interaction and the effects of zolpidem with SBE-CD and the chitosan ingredient as claimed in the present invention, one skilled in the art would not have been able to derive the presently claimed invention from any combination of the prior art cited by the Examiner, let alone have been able to have an objectively reasonable expectation of success.

Reconsideration and withdrawal of all of the obviousness rejections are respectfully requested.

Upon reconsideration and withdrawal of all of the rejections and a rejoinder of the non-provisionally elected claims, an early Notice of Allowance of all of the pending claims is also respectfully requested.

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